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Original Article

Evaluation the role of supplementation of oral zinc on systolic and diastolic blood pressure in type 2 diabetic patients

Khan S[1], Rana MSA[2] , Haque MF[3] , Tanni SF[4] , Tabassum S[5]

Abstract

Background: *Zinc is an important trace element and a potent antioxidant. Its deficiency causes a common comorbidity with numerous chronic diseases including hypertension and diabetes mellitus, associated with development and progression of various complications.* ***Objective:*** *The present study has been undertaken to evaluate the effects of zinc supplementation on blood pressure in type 2 diabetic patients.* ***Methods:*** *This prospective interventional study was conducted in the Department of Physiology, Dhaka Medical College, Dhaka between January 2016 to December 2016. In this study, a total number of 46 diagnosed type 2 diabetic patients of both sexes were selected with age ranging from 40 to 55 years. Among them, 26 type 2 diabetic patients with supplementation of oral zinc (40mg/day) for 12 weeks were considered as study group (Group B). Another 25 age matched type 2 diabetic patients without supplementation of oral zinc were considered as control group (Group A) for comparison. All subjects were selected from Outpatient Department of Endocrinology, Dhaka Medical College Hospital, Dhaka on the basis of inclusion and exclusion criteria. Their blood pressure (BP) was measured and serum zinc level was estimated by Spectrophotometric method accordingly. These parameters were studied 2 times in all subjects of control and study groups i.e. at the beginning of study (base line) and after 12 weeks of study period. Data were collected in pre-designed structured questionnaire form by the researcher herself. For statistical analysis, paired Student's 't' test and unpaired Student's 't' test were performed as applicable using SPSS for windows version 22.0.*

Results: *In this study, after zinc supplementation resulted in a significant ($p<0.001$) decrease in both systolic and diastolic blood pressure in study group but there was no significant change observed in control group.* ***Conclusions:*** *After analyzing the results of the study, it can be concluded that oral zinc supplementation can be useful for improving blood pressure in type 2 diabetic patients.*

Key words: *Type 2 Diabetes mellitus, Blood pressure, Zinc.*

Introduction: Diabetes mellitus is a clinical syndrome characterized by hyperglycemia caused by relative or absolute deficiency of insulin in the body[1].There are two general types of DM, one is type I or insulin dependent diabetes mellitus (IDDM) and other is type II or non-insulin dependent diabetes mellitus (NIDDM). Among them, type II diabetes is more common and about 90 to 95 % of all cases of DM[2]. According to American Diabetes Association (2016), diagnostic criteria of diabetes mellitus are fasting blood glucose level ≥7.0 mmol/L (126mg/dl) or 2 hours after 75gm glucose ≥11.1mmol/L (200mg/dl) or HbA1c ≥6.5[3]. According to International Diabetes Federation, it is the fourth leading cause of death in most of the high income countries[4]. World Health Organization (WHO) estimated that about 180 million diabetes mellitus patients worldwide during 2000 and expected to be increased to 399 million by the year 2030 [5]. According to International Diabetic Federation (IDF), there were 382 million people had diabetes in 2013 and by the year 2035, this will rise to 592 million,

1. ***Dr. Sharmin Khan,*** Associate Professor, Department of Physiology, Mainamoti Medical College, Cumilla
2. ***Dr. Md. Saiful Ahsan Rana,*** *Medical officer, Department of Nephrology, 500 bedded general hospital, Mugda, Dhaka.*
3. ***Dr. Mohammad Fazlul Haque,*** *Vice Principal & Associate Professor, Department of Physiology, Central Medical College, Cumilla.*
4. ***Dr. Shomia Farid Tanni,*** *Assistant Professor, Department of Physiology, Mainamoti Medical College, Cumilla.*
5. ***Dr. Sabira Tabassum,*** *Assistant Professor (CC), Department of Physiology, Delta Medical College, Dhaka.*

Correspondence : ***Dr. Sharmin Khan,*** *Email: sharmin.bmch@gmail.com. 01715988062*

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whereas the national prevalence in Bangladesh is about 5.52%[6]. In Diabetes mellitus, chronic hyperglycemia produces macrovascular complications like coronary artery disease, peripheral arterial disease, stroke and microvascular complications like retinopathy, nephropathy, neuropathy [7].

Hypertension is a condition where sustained raise of systolic blood pressure >140mmHg and diastolic blood pressure >90 mmHg, measured in two separate occasions. Now a day's hypertension has become a global health problem, about 1.13 billion people have hypertension is worldwide. Risk factors for development of hypertension includes high salt intake, low essential trace elements like zinc, less physical activity, smoking, stress etc[8,9,10].

Diabetes mellitus may affect the homeostasis of trace elements. It causes significant decrease in some trace elements which leads to development of diabetic complications[11]. Zinc is an essential trace element with multiple roles in human nutrition. Zinc is inevitable for maintaining optimum health because of its diverse metabolic functions. It acts as a cofactor of more than 300 enzymes and over 200 metallo-enzymes. Zinc is required for various cellular process including DNA and protein synthesis and intracellular signaling [12, 13]. It plays an important role in antioxidant defense and in the metabolism of carbohydrate, fat and protein [11]. Zinc is an important trace element that is directly involved in synthesis, storage, secretion and action of insulin. It helps to increase the binding ability of insulin to its receptor and thus facilitates transport of glucose into cell and its deficiency leads to insulin resistance and impaired glucose tolerance[14].

Within beta cell, proinsulin is converted into insulin monomer in presence of zinc. Thus, zinc is essential for processing, synthesis, storage and secretion of insulin from beta cell[13]. Hyperglycemia can interfere the active transport of zinc back into tubular cells of kidney causing hyperzincurea[15]. Thus the lower level of zinc may decrease the production, secretion and action of insulin from pancreatic islets cells[16,17]. So, zinc has insulin-mimetic action .It enhances glucose uptake into cell leading to lowering blood glucose level. Thus, zinc promotes insulin signaling pathway [18, 19, 20, 21]. Thus, zinc lowers blood glucose level by utilizing glucose that potentiates insulin activity[22, 23], [24, 25].

Hypertension is an important major risk factor that are responsible for various detrimental diseases associated with many life threatening conditions like cardiovascular disease (CVD), cerebrovascular disease, chronic kidney disease etc. chronically elevated sustained blood pressure causes increase cardiac output and endothelial damage leading to lethal medical conditions. Zinc is an important co factor for superoxide dismutase (SOD) enzyme which helps to remove free radical mediated toxins from body and protects the body by scavenging excess superoxide. So, zinc is an important component of body's antioxidant system which decreases the complications related to oxidative stress in diabetes and gives protection against immune mediated free radical attack[26]. Zinc supplementation enhancing production of nitric oxide (NO) which is a potent vasodilator and superoxide dismutase (Zn-SOD) which protects vascular endothelium. Zinc also causes suppression of inflammatory cytokines. AS a result it maintains the vascular tone. Zinc causes production and activation of angiotensin converting enzyme (ACE) which in turn controls cardiac output and heart rate. It also causes increase excretion of sodium by modulating Na/K ATPase activity. Thus, expressing its diuretic activity[27,28]. Low zinc level causes increased reabsorption of renal sodium in distal convoluted tubules of kidney, leading to increased bloodpressure[2930,31]. So, zinc supplementation with dietary management may be beneficial as therapeutic strategy in hypertension and insulin resistence[32].

Methods:

This prospective interventional study was conducted in the Department of Physiology, Dhaka Medical College, Dhaka from January 2016 to December 2016. Protocol of this study was approved by Ethical Review Committee of Dhaka Medical College, Dhaka. Among 51 diagnosed type 2 diabetic patients, 5 patients were excluded and 46 patients completed the study. For this study, these 46 diagnosed type 2 diabetic patients of both sexes were selected with age ranging from 40 to 55 years. Among them, 21 type 2 diabetic patients with supplementation of oral zinc (40mg/day) for 12 weeks were considered as study group (Group B). Another 25 age matched type 2 diabetic patients without supplementation of oral zinc were considered as control group (Group A) for comparison. They were selected from outpatient department of Endocrinology, Dhaka Medical College Hospital, Dhaka. After selection of the subjects, the nature,

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purpose and benefit of the study were explained to each subject in details. Informed written consent was taken from the participants. All the information's were recorded in a prefixed data collection form. Patients having ischemic heart disease, chronic kidney disease, chronic liver disease, patients with a history of stroke/infection/diarrhea, patients with any types of malignancy, patients receiving zinc supplementation or medications influencing serum zinc level were excluded from the study. For blood pressure measurement, the subject was asked to sit in an armed chair for 15 minutes in a quiet room with comfortable room temperature. Then blood pressure was recorded 2 times by asucultatory method by using standard sphygmanometer and the mean value is taken for analysis.

Serum Zinc level was measured by using flame atomic absorption of spectrophotometer in spectrophotometric method in Institute of Nutrition and Food Science, University of Dhaka. This parameter was studied 2 times in all subjects of control and study group, i.e., at the beginning of study (base line) and after 12 weeks of study period. Type and dose of oral hypoglycemic & antihypertensive drugs, diet, and physical activity of the patients remained unchanged during the course of study.

Data analysis

This parameter was expressed as mean ± SD (standard deviation) and range. Paired Student's 't' test and unpaired Student's 't' test were used as the tests of significance as applicable. The p value < 0.05 was accepted as level of significance. Statistical analyses were performed by using a computer based statistical program SPSS (Statistical package for social science) version 22.0.

Results:

General characteristics are presented in table I. In this study, after zinc supplementation resulted in a significant (p<0.001) decrease in both systolic and diastolic blood pressure in study group but there was no significant change observed in control group (Table II and figure1,2).

Table I: General characteristics of the subjects in both groups (n=100)

Parameters	Group		*p* value
	Group A Healthy subjects (n =50)	Group B Diabetic patients (n =50)	(A vs B)
Age (years)	45.64 ± 4.23	47.06 ± 4.63	0.113^{ns}
	(40 - 54)	(40 - 55)	
Sex			
Male	24 (48.0)	22 (44.0)	
Female	26 (52.0)	28 (56.0)	
BMI (kg/m^2)	25.77 ± 3.59	25.77 ± 4.12	0.998^{ns}
	(18.03 – 38.23)	(16.42 – 39.00)	
Systolic BP (mmHg)	116.20 ± 9.97	122.70 ± 12.42	
	(90 - 130)	(100 - 140)	
Diastolic BP (mmHg)	76.40 ± 7.69	78.70 ± 7.61	
	(60 - 90)	(60 - 90)	

Results are expressed as mean ± SD. Figure in parentheses indicate range. Unpaired Students't' test was performed to compare between groups. The test of significance was calculated & p value < 0.05 was accepted as level of significance.
n = number of subjects
ns = not significant

Table II: Blood Pressure (SBP & DBP) levels in different groups (n=46)

Parameters	Groups			
	A_1 (n=25)	A_2 (n=25)	B_1 (n=21)	B_2 (n=21)
SBP (mm of Hg)	132.40 ± 8.18	132.60 ± 9.14	137.14 ± 8.88	126.42 ± 9.10
DBP (mm of Hg)	86.20 ± 4.39	87.60 ± 5.79	88.71 ± 5.02	84.04 ± 4.36

Statistical analysis

Groups	*p* value	
	SBP	DBP
A_1 vs A_2	0.870^{ns}	0.070^{ns}
A_1 vs B_1	0.066^{ns}	0.077^{ns}
B_1vs B_2	<0.001***	<0.001***
A_2 vs B_2	0.027*	0.026*

Results are expressed as mean ± SD. Paired t test was performed for comparison within groups and unpaired t test was performed to compare between groups. The test of significance was calculated &

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p value < 0.05 was accepted as level of significance.
n = number of subjects
ns = non significant
*/**/*** = significant
A1: Control group (Type2 DM at baseline)
A2 : Control group (Type 2 DM after 12 weeks)
B1: Study group (Type 2 DM at baseline)
B2: Study group (Type 2 DM with zinc supplementation after 12 weeks)

Figure 1: Mean systolic blood pressure (SBP) level in groups level in groups (n=46)

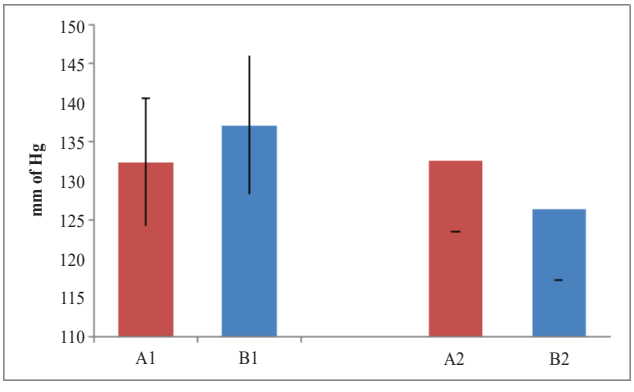
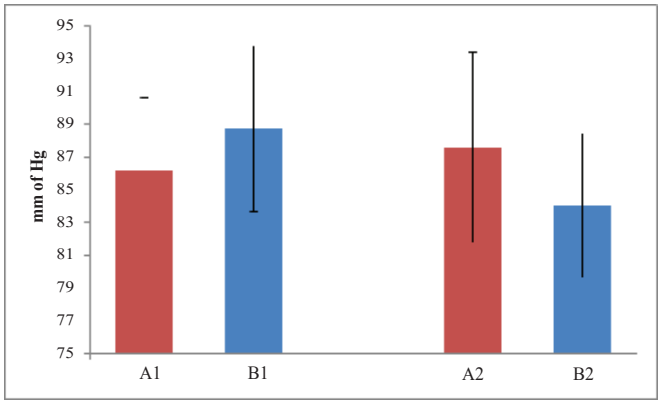


Figure 10: Mean diastolic blood pressure (DBP) level in groups level in groups (n=46)



Discussion:

Hypertension is one of the essential leading causes of mortality and morbidity now a day. Deficiencies of trace elements, such as zinc deficiency are an independent risk factor for development of hypertension and its associated complications33. This prospective interventional study was carried out to explore the association of serum zinc with hypertension. In this study, no significant gender difference was observed between the groups. Type 2 DM, hypertension and serum zinc level presents a complex relationship which exhibits lower zinc status.

As a result of normal metabolic process, free radicals are continuously produced in human body. And there are antioxidant defense mechanisms (such as superoxide dismutase-SOD) also present in human body to combat the adverse effects of these free radicals. These free radicals are unstable and react with lipid bilayer of cell membrane causing lipid peroxidation which reduces antioxidant activity.

Zinc is an important co factor for superoxide dismutase (SOD) enzyme which helps to remove free radical mediated toxins from body and protects the body by scavenging excess superoxide. In type 2 diabetes, there is increased generation of reactive oxygen species and free radical activity causes lipid peroxidation which leads to development of microvascular and macrovascular diabetic complications [34]. In this study, we have found that the mean systolic and diastolic level were significantly ($p<0.001$) lower in diabetic patients after 12 weeks of supplementation with oral zinc in comparison to that of their baseline value. In current study, the result is in agreement with previously published data that showed improvement in blood pressure after supplementation of oral zinc[35,36]. However, this finding was not in consistent with the findings of previous study who found no significant difference in blood pressure in patients after supplementation of oral zinc in comparison to that of their base line value and diabetic control group who were not supplemented with oral zinc[37].

Therefore, any alteration of serum zinc level may affect the activity of SOD, which ultimately causes vascular endothelial dysfunction[38,39]. On the contrary ,zinc have a negative effect on ATP-dependent Ca 2+ channel that causes efflux of calcium ions from inside of the cell [40]. that leads to an elevation of arterial wall tension. These effects together results in development of hypertension[41]. Therefore, serum zinc level acts as an important tool in management of hypertension.

Conclusions:

From the results of the study, it can be concluded that oral zinc can decrease the blood pressure in patients with type 2 diabetes mellitus. Therefore, estimation of serum zinc level and supplementation of oral zinc in routine management may be helpful to minimize the complications in type 2 diabetes mellitus with hypertension.

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Limitation:

• The study was conducted in a selected hospital. So, the study population might not represent the whole community.

Recommendation:

• Similar type of study can be done with large sample size.

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